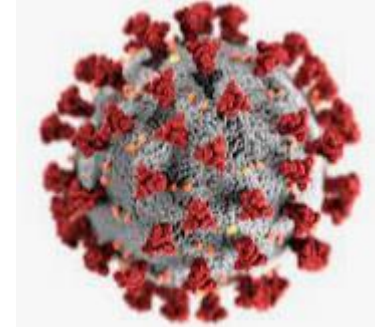


بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

*In the Name of God, the  
Compassionate, the Merciful*

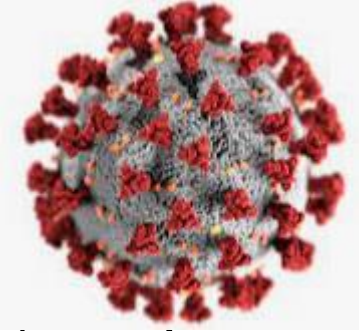


# Central Nervous system manifestation in adult patients with COVID-19

Vahid Reza Ostovan

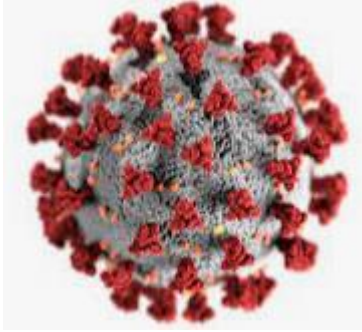
Shiraz University of Medical Sciences

# *Introduction*

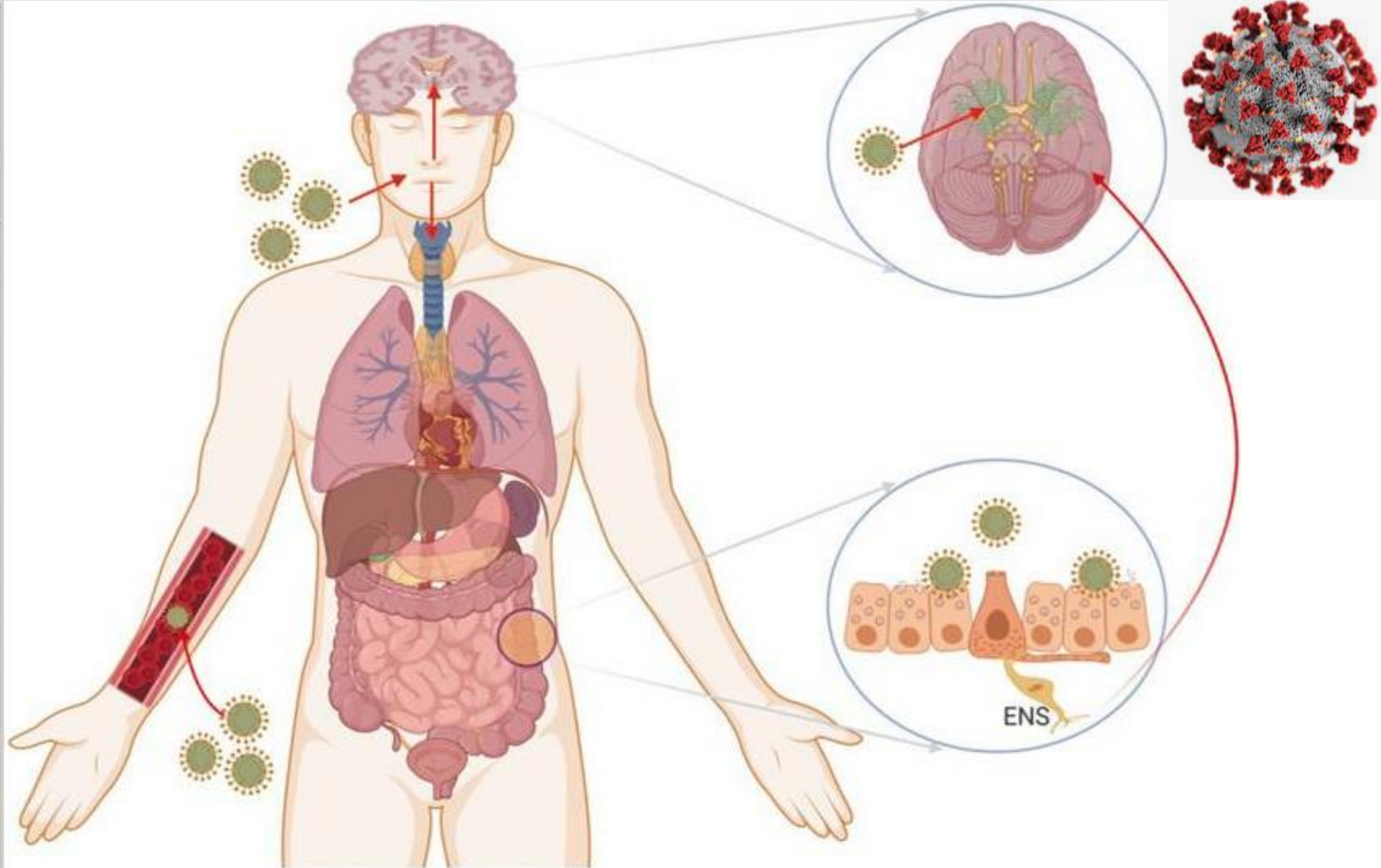


- The COVID-19 is a single-stranded positively sensed RNA virus, consisting of 26–32 kb-sized genome
- The average diameter is 100 nm, spherical, or oval-shaped.
- COVID-19 is externally covered by a crown shaped like spike (S) proteins, which also can mutate frequently.
- These characteristics illustrate the adaptability of the virus to change its infectivity over time.
- The angiotensin-converting enzyme 2 (ACE2) receptors, which normally helps to regulate blood pressure, is abundantly expressed in the lungs. The spike proteins of the COVID-19 bind to ACE2 receptors to invade the cell and develop the infection.

# *Pathophysiology of CNS involvement in COVID-19*

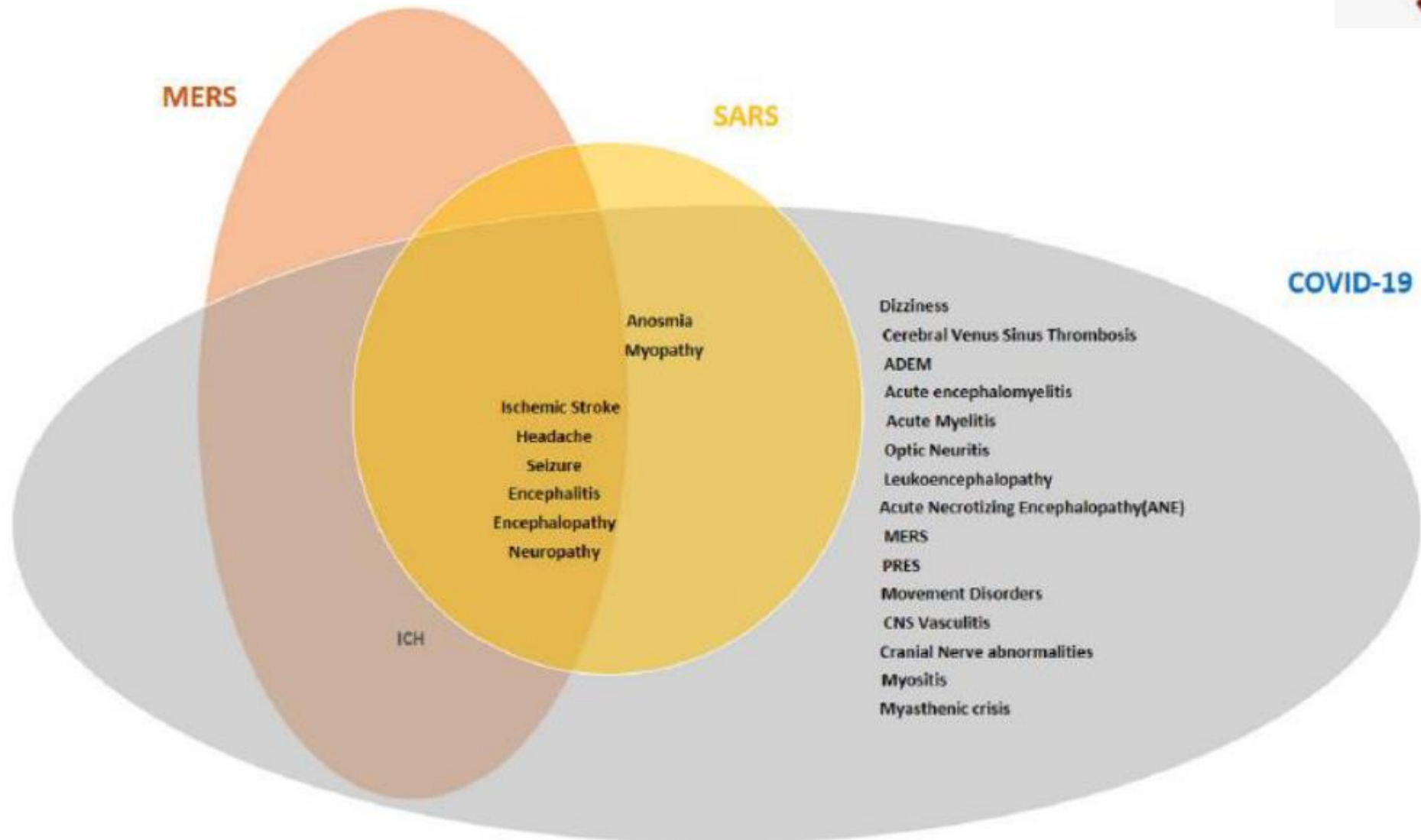
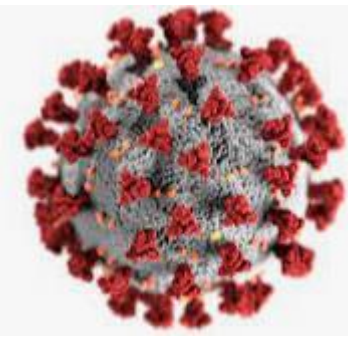


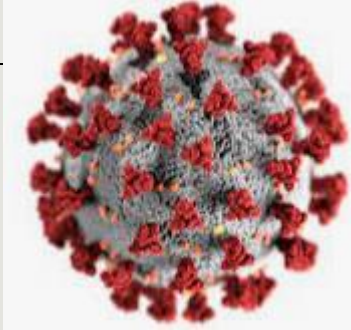
- **Direct invasion**
  - Retrograde axonal neuronal transport through olfactory nerve and ENS(enteric plexus)
  - Endothelial dysfunction —————> Blood-Brain-Barrier dysfunction Neuronal —————> invasion via ACE 2 receptor
- **Cytokine storm**
- **Pneumonia**
- **Immune Dysregulation due to HPA** (hypothalamic-pituitary-adrenocortical axis)





# Neurological manifestations in different COV infection





### Neurological symptoms reported in COVID-19 patients

- Dizziness
- Headache
- Obtundation
- Hypogeusia
- Ageusia
- Hyposmia
- Anosmia
- Myalgia

### Neurological disorders reported to occur with COVID-19

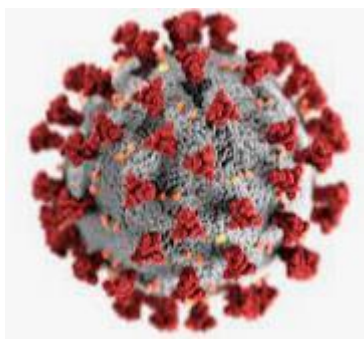
- Stroke (ischaemic, haemorrhagic, secondary to coagulopathy)
- Sinus venous thrombosis
- Cerebral haemorrhage
- Encephalopathy
- Altered mental status
- Meningitis
- Encephalitis
- Febrile seizures
- Acute haemorrhagic necrotizing encephalopathy

- Acute disseminated encephalomyelitis
- Myelitis
- Myasthenia gravis
- Miller–Fisher syndrome
- Guillain–Barré syndrome
- Polyneuritis cranialis

### Neurological patients at risk in the context of COVID-19

- Alzheimer disease
- Parkinson disease
- Motor neuron disease
- CNS disorders with reduced mobility or immobility
- Neuromuscular disorders with reduced mobility and compromised respiratory function
- Autoimmune conditions
  - Multiple sclerosis
  - Neuromyelitis optica spectrum disorders
  - Myasthenia gravis
  - Guillain–Barré syndrome
  - Chronic dysimmune neuropathies

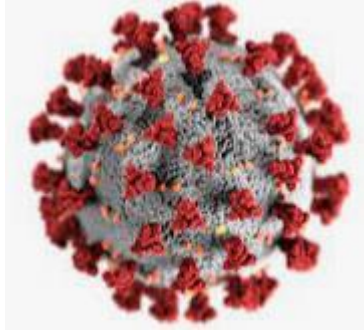
# Headache



- The most frequent neurological symptoms of COVID-19.
- The prevalence of Headache in COVID-19 varied from 10%-70% in different studies.
- Headache is more frequent and intense in female.
- In 50% of patients, there is PMH of headache (18% migraine, and 23% TTH).
- Headache started within the first day of symptoms of COVID-19 (41%) of patients, and in first four day in 75% of patients.
- Headache persisted longer than 1 month of after the resolution of the general COVID-19 symptoms in 13% of patients.
- Headache has a moderate to severe intensity in most patients.
- Headache occurs more frequently bilateral (80%), in frontal region (71%) with pressing quality (75%).
- Red flags of headache are present in 61% of cases.

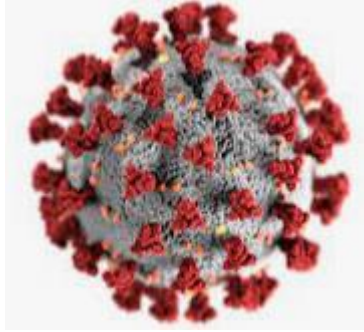


# Headache



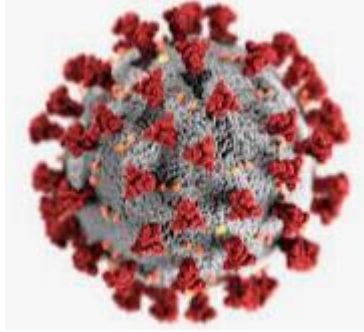
- Direct invasion of SARS-CoV-2 to the trigeminal nerve endings in the nasal cavity.
- Trigemino-vascular activation due to involvement of the endothelial cells of the vessel walls with high expression of angiotensin-converting enzyme 2 (ACE2).
- Release of the pro-inflammatory mediators and cytokines during COVID-19 might stimulate the perivascular trigeminal nerve endings.

# Dizziness



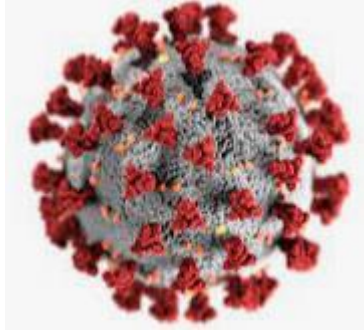
- Dizziness is reported in **4-30%** of COVID-19.
- Lightheadedness (44%), disequilibrium(28%), presyncope (16%), vertigo(12%).
- Twice more frequent in female than male.
- Lightheadedness: 1-psychological 2- hypoglycemia
- Syncope: 1- viral myocarditis 2- adrenergic denervation 3- autoimmune autonomic neuropathy 4- dehydration
- Vertigo: 1-BPPV 2- vestibular neuritis and labyrinthitis 3- Menière's disease 4- vestibular migraine 5- cerebellitis

# Cerebrovascular disease



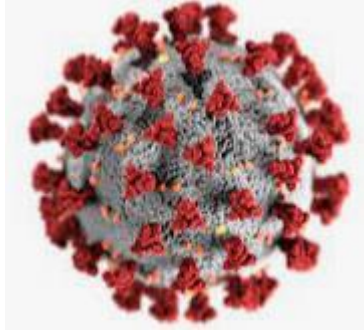
- Ischemic stroke
  - The prevalence of IS ranges from 0.4-4.6% in different cohort studies.
  - Cryptogenic stroke was the most common subtype of IS in COVID-19 patients(35% of all cases of COVID-19 associated-IS).
  - Decreased prevalence of lacunar infarction ( $\leq 10\%$ ) among COVID-19 associated-IS patients.
  - COVID-19 positive patients with large vessel occlusion are younger than those without COVID-19.
  - Cryptogenic stroke is the most prevalent type of stroke among COVID-19 patients.

# *Cerebrovascular disease*



- Cerebral hemorrhage
  - ICH, SDH, SAH
  - The prevalence of cerebral hemorrhage ranges from 0.1-0.9% in different cohort studies.
  - COVID-19 patients with ICH are younger than patients with non-COVID ICH and mostly suffered from lobar and multifocal ICH.
  - Coagulopathy is the most common etiology.

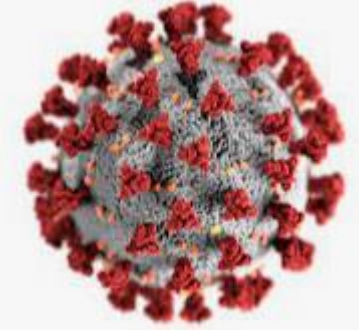
# *Cerebrovascular disease*



- Cerebral venous sinus thrombosis
  - Headache and impaired consciousness may complicate or even be the presenting symptoms of both COVID-19 and CVST.
  - Persisting headache and altered consciousness with confusion and/or agitation, coupled with high levels of D-dimers ( $>2\text{ng/ml}$ ).
  - CVT involving the internal cerebral veins may be challenging to differentiate from acute hemorrhagic necrotizing encephalitis (Weston–Hurst syndrome).

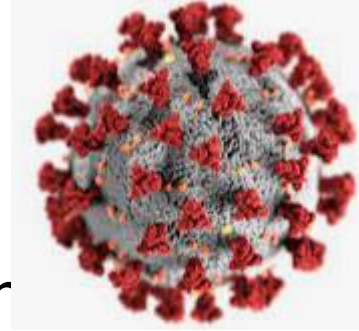


# *Cerebrovascular disease*



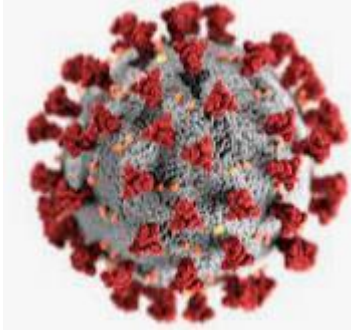
- **Targeting angiotensin-converting enzyme 2 (ACE2) receptor**
- **Cardiovascular complications associated with COVID-19**
- **Coagulopathy associated with COVID-19**
- **Triggering CNS vasculitis and endotheliitis**
- **Critical illness due to COVID-19**

# *Decrease level of consciousness (DOC)*



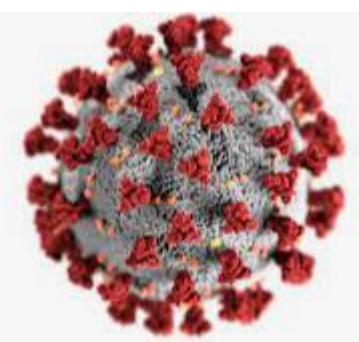
- Impaired consciousness was observed in **1% to 20%** of patients with COVID-19, mostly in patients with severe infection and comorbid conditions.
- The etiology of COVID-DoC is multifactorial : Structural brain injury, medical causes of encephalopathy, systemic inflammation, hypoxemia, and the effect of sedation may all play a role, to varying degrees, in COVID-DoC.

# *Encephalitis*



- Encephalitis can presents weeks after the onset of symptoms of COVI or the symptoms of COVID-19 and encephalitis occurs at the same time.
- Fever (70.37%), altered mental status (53.70%), decreased consciousness/unconsciousness (33.33%), seizure (29.62%), headache (20.37%), weakness/asthenia (18.51%), psychiatric symptoms (14.81%), myalgia (7.40%), and myoclonus (5.55%).
- Brain MRI (81.48%), CSF analysis (46.29%), electroencephalography (42.59%), and head CT (37.03%) were the most frequently used methods to diagnose encephalitis

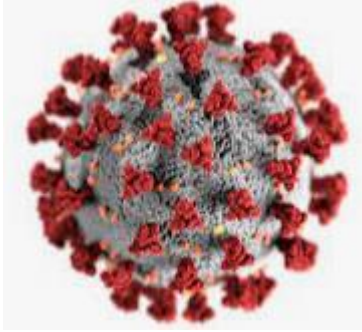
# Encephalitis



- The most common MRI patterns in COVID-19 associated encephalitis are hyperintensity in the white matter (44.68%), hyperintensity in the temporal lobe (17.02%), and hyperintensity of the thalamus (12.76%).
- Among the analysis performed on CSF, only 79.41% were positive.
  - This negative results may be due to the different mechanisms or performing CSF analysis in the early stages of the disease.
- Treatment include hydroxychloroquine (50%), acyclovir (20%), ritonavir/lopinavir (16.66%), IV methylprednisolone/oral prednisone (36.11%), IV immunoglobulin(27.77%).
- Mortality rate of COVID-19 associated encephalitis is 28.26%.

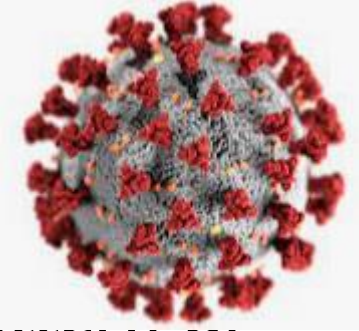
# *Demyelinating disorders*

- ANE (acute necrotizing encephalitis)
- ADEM(acute disseminated encephalomyelitis)
- MS-like
- NMO-SD
- MOGAD
- Optic neuritis
- TM(transvers myelitis)



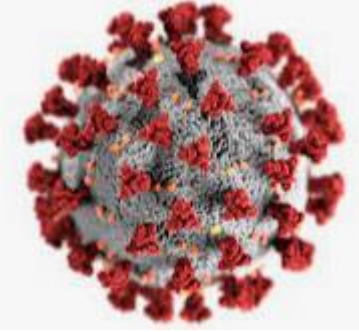


# *Demyelinating disorders*



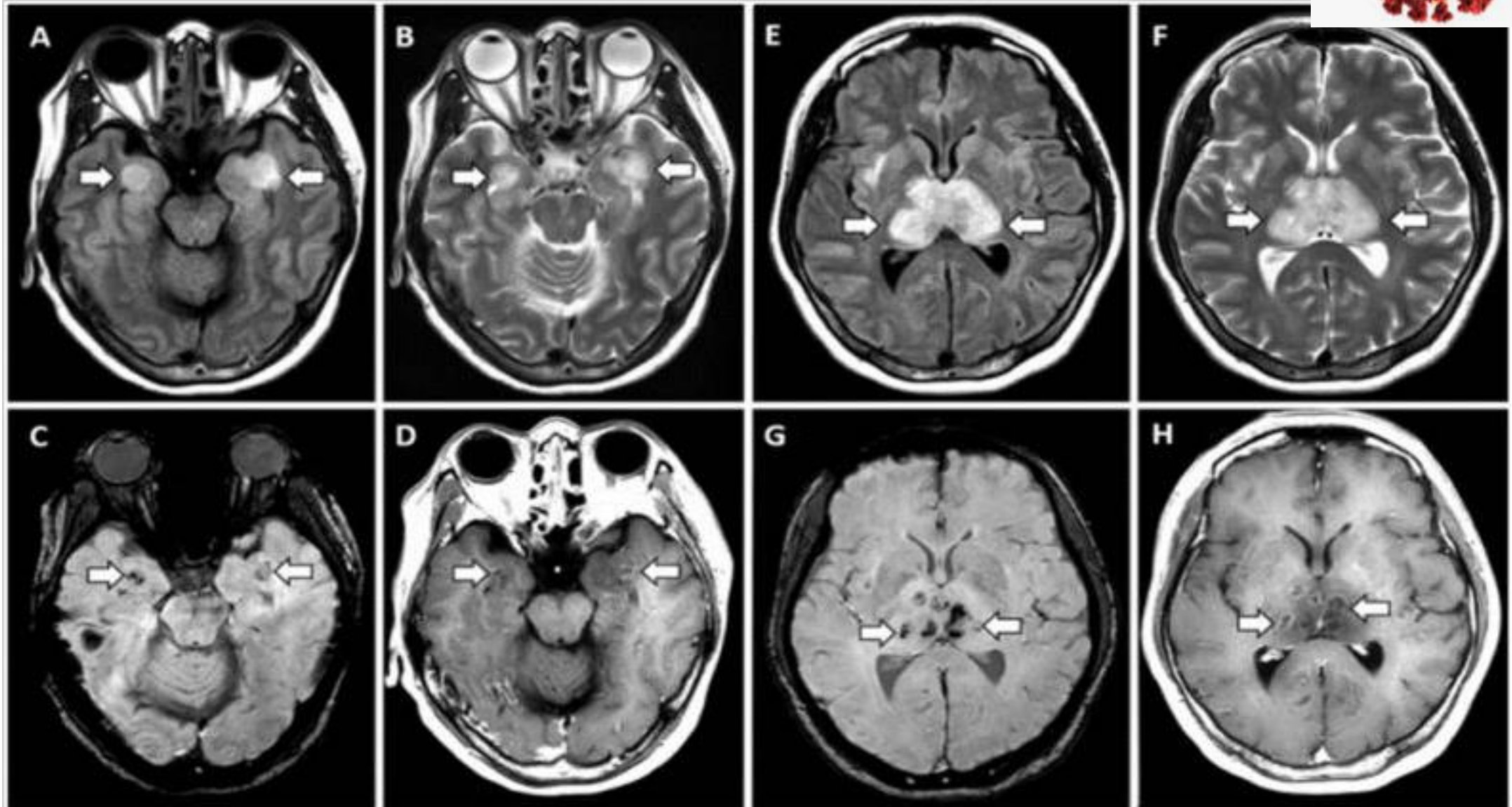
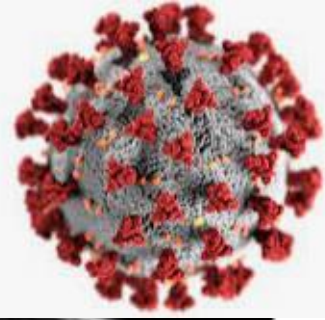
- Encephalitis/encephalomyelitis is the most common (90%) pattern of COVID-19 associated CNS demyelination.
- MS, NMOSD and even MOGAD are accounted for about 10%.
- The pathophysiologic mechanisms include: 1- Direct viral invasion to the CNS 2- Immune-mediated process triggering other well-known conditions 3- Sequel for hypoxia affecting the CNS as a direct result of respiratory affection.

# *Encephalitis/encephalomyelitis*

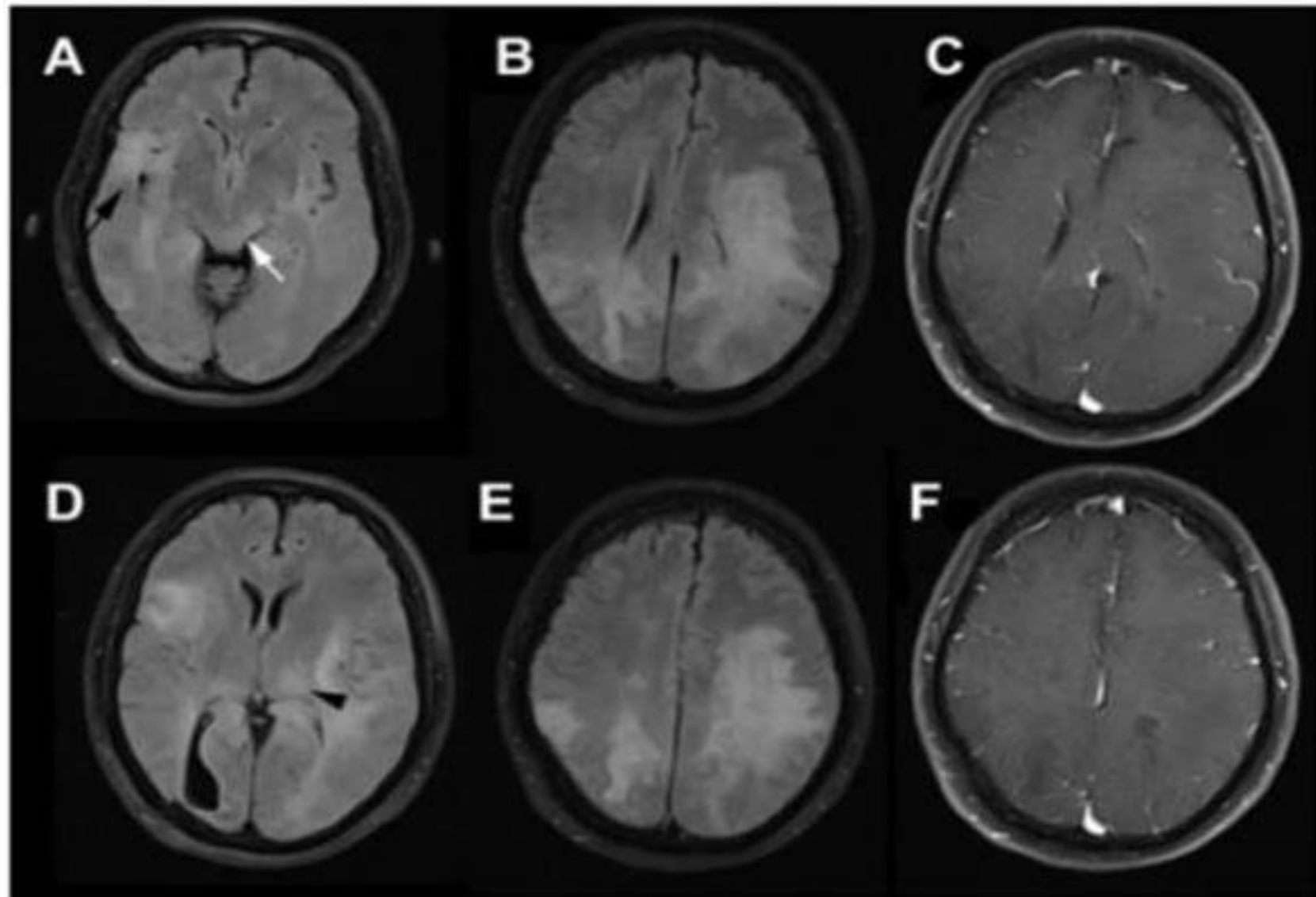
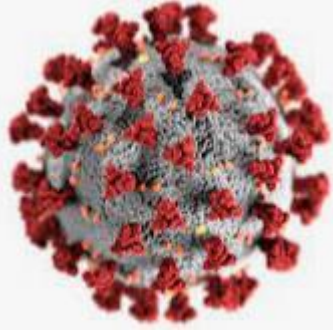


- Lethargy, loss of consciousness and/or seizures are the most common clinical findings.
- The symptoms related to demyelinating disorders might occur at initial presentation of COVID-19 infection or within the following few weeks.
- Hemorrhage and/or necrosis are reported in **36.6%** of these patients, especially more frequent in those with severe COVID-19 infection requiring mechanical ventilation.

# Acute Necrotizing Hemorrhagic Encephalitis

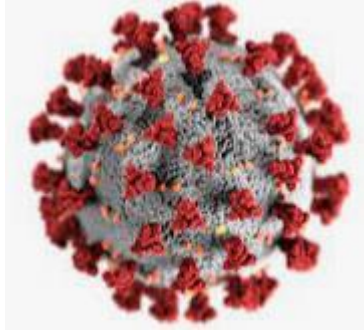


# ADEM





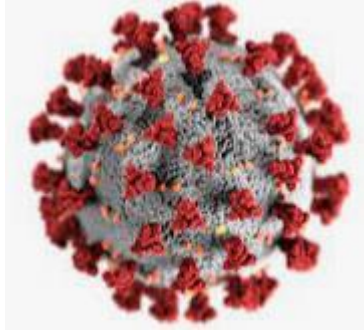
# *MS-like/NMOSD/MOGAD*



- OCB is positive in most cases of COVID-19 associated MS.
- Atypical clinical presentation and radiological findings are more common in COVID-19 associated MS (raising concern about diagnosis, it is true MS or only post infectious demyelination?)
- LETM with cerebral lesions are common findings in COVID-19 associated NMOSD.
- MOGAD more commonly presented with bilateral optic neuritis or ADEM.

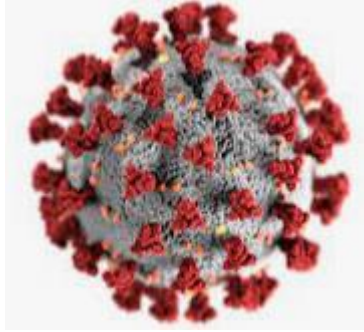


# *Transverse myelitis*



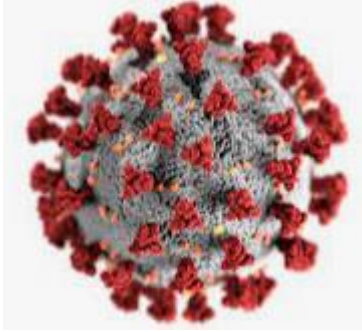
- LETM was the most frequently reported pattern of spinal involvement reported in 72.5% of cases of myelitis.
- The pathophysiologic mechanisms include: acute viral myelitis, post-COVID-19 immune-mediated myelitis, ischemic myelitis, part of an inflammatory demyelinating syndrome triggered by COVID-19 infection (ADEM, MS, NMOSD, and MOGAD).
- IV MTP, PLEX, IVIg, and rituximab can be prescribe in the treatment of COVID-19 associated myelitis.

# *Leukoencephalopathy*



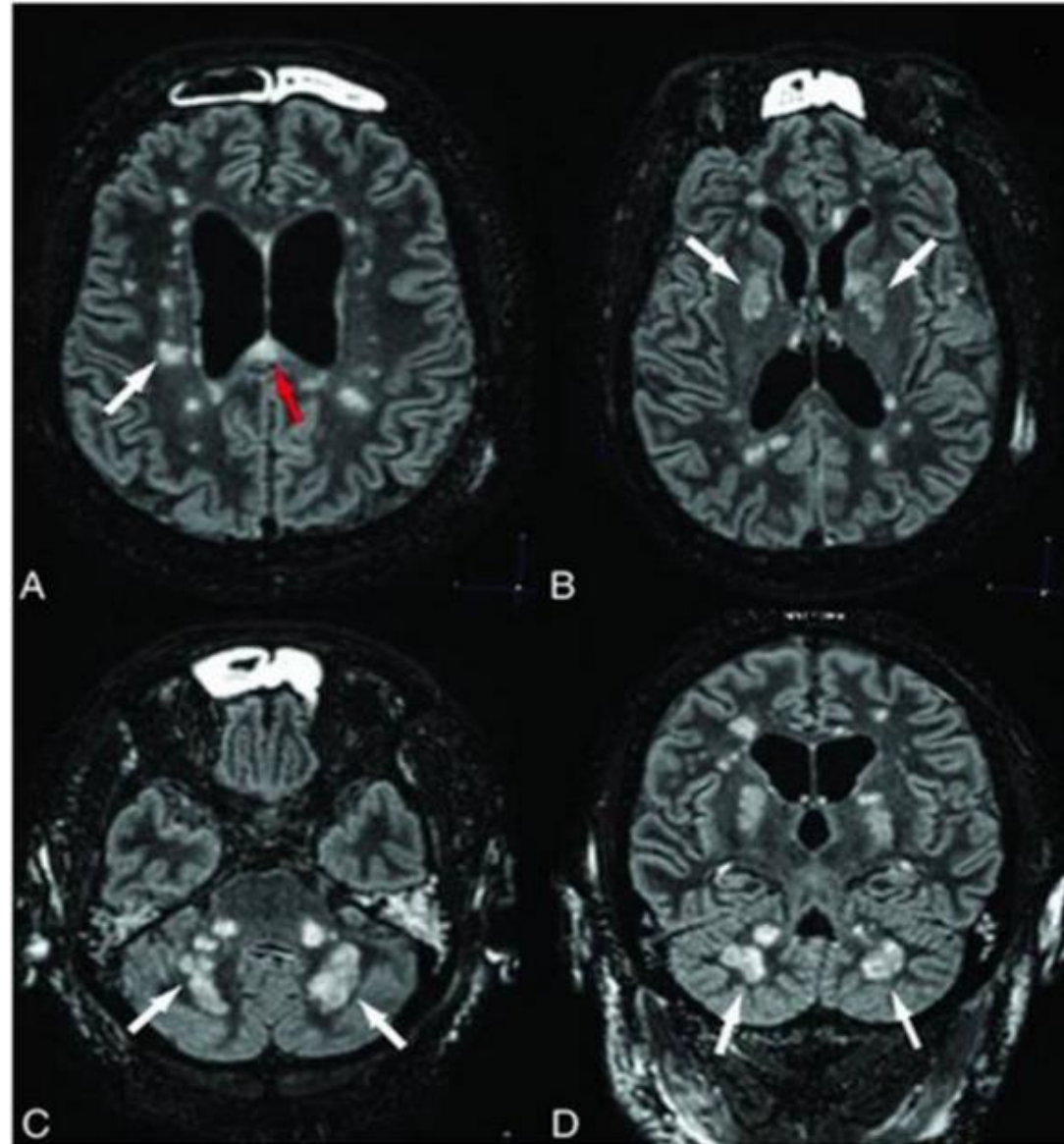
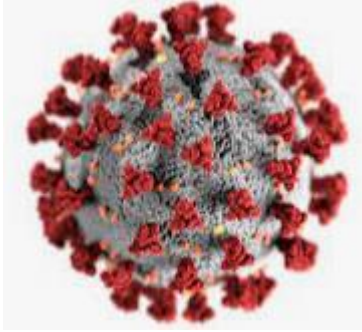
- DPHL (delayed post hypoxic leukoencephalopathy)
- Direct cerebral infection
- Post-infectious demyelination
- Posterior reversible encephalopathy syndrome (PRES)

# *PRES*

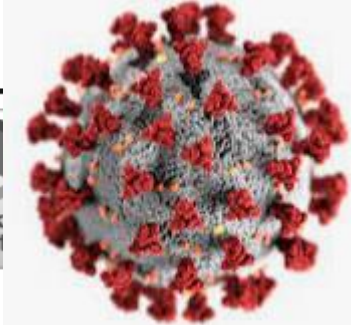


- PRES presents with acute impairment in level of consciousness, headache, visual disturbance and seizures.
- Cortical and subcortical vasogenic edema, involving predominantly the parietal and occipital regions bilaterally.
- Endothelial dysfunction related to SARS-CoV-2 in combination with hemodynamic instability and immunological activation with release of cytokines (cytokine storm) may increase the vascular permeability in the brain tissue.


# *CNS vasculitis*







## A First Case of Acute Cerebellitis Associated with Coronavirus Disease (COVID-19): a Case Report and Literature Review

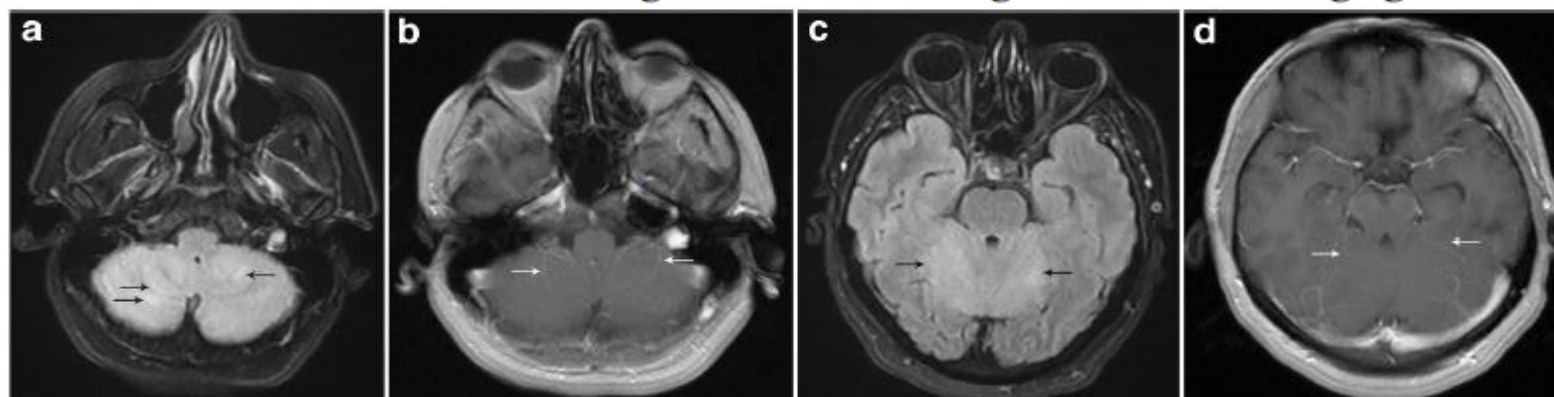
Nima Fadakar<sup>1</sup> · Sara Ghaemmaghmi<sup>1</sup> · Seyed Masoom Masoompour<sup>2</sup> · Babak Shirazi Yeganeh<sup>3</sup> · Ali Akbari<sup>4</sup> · Sedighe Hooshmandi<sup>5</sup> · Vahid Reza Ostovan<sup>1</sup> 

© Springer Science+Business Media, LLC, part of Springer Nature 2020

### Abstract

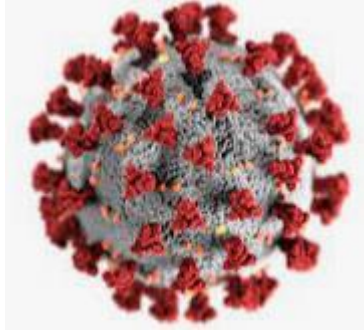
Novel coronavirus (severe acute respiratory syndrome-coronavirus-2: SARS-CoV-2), which originated from Wuhan, China, has spread to the other countries in a short period of time. We report a 47-year-old male who was admitted to our hospital due to suffering from progressive vertigo and ataxia for 7 days prior to the admission. Neurological examination revealed cerebellar dysfunction, and brain magnetic resonance imaging (MRI) depicted edema of the cerebellar hemisphere associated with leptomeningeal enhancement. Cerebrospinal fluid (CSF) analysis showed mild lymphocytic pleocytosis, elevated protein, and lactate dehydrogenase. SARS-CoV-2 RNA was detected in the oropharyngeal/nasopharyngeal and CSF specimens. As a result, treatment with lopinavir/ritonavir was initiated, and patient symptoms and signs improved significantly during the course of hospitalization. To the best of our knowledge, this is the first case of acute cerebellitis associated with COVID-19 disease which is reported in the literature so far.

**Keywords** COVID-19 · SARS-COV-2 · Ataxia · Vertigo · Cerebellitis · Magnetic resonance imaging





# Seizure



- Incidence of acute symptomatic seizures due to COVID-19 is as less than 1%.
- 70-90% of them are new-onset seizures, and 10-30% occurred in patients with a previous history of controlled epilepsy.
- The pathophysiologic mechanisms include hypoxia, metabolic derangements, organ failure, or cerebral damage.
- There was a previous history of cognitive impairment, older age, and higher levels of creatine-kinase and C-reactive protein in patients with COVID-19 and seizure.
- In patients with baseline epilepsy, SARS-CoV-2 infection may trigger seizures; therefore, it is ideal to anticipate breakthrough seizures and prescribe short-term anti-seizure medications appropriately.

*Thanks for Your Attention*

